Carbohydrate Research 407 (2015) 51–54

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Note

Room-temperature ionic liquids enhanced green synthesis of β-glycosyl 1-ester

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ARTICLE INFO

Article history:
Received 29 April 2014
Received in revised form
17 January 2015
Accepted 21 January 2015
Available online 29 January 2015

Keywords:
Glycosyl ester
Ionic liquid
Silver oxide
Green glocosylation
Glycosyl bromide

ABSTRACT

We herein report an efficient synthesis of β-glycosyl 1-ester in room-temperature ionic liquids (RTILs) promoted via silver salt and quaternary ammonium salt (PTC) with good or excellent yields. All products were isolated exclusively as the β-anomers. Four different RTILs, eight metal salts and four quaternary ammonium salts were screened in the glycosylation reaction. The synergistic effect of C_6mim·OTf, Ag_2O and tetrabutylammonium iodine gave the best results. Their promotion to the system was integral. Thorough study provided insight into the catalytic activity of ionic liquid structure, metal salts and quaternary ammonium salt to these reactions. It is worth mentioning that the yield of aliphatic compound 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl butyrate (**3l**) was highly improved when using C_6mim·OTf as solvent compared with the normal volatile solvents under the same catalysts. This green approach has been proved to be practical and compatible with a wide range from aliphatic to aromatic substrates.

The exploration of stereocontrolled glocosylation was driven by the biological application of carbohydrates. It promoted numerous advances in donor, acceptor, promoter, and solvent technology for stereocontrolled glycosylation.[1] Eco-friendly ionic liquids as solvents and promoters often demonstrate higher product yields, control over reaction stereoselectivity, and recyclability of the IL solvent.[2] Recently, the utilization of highly polar room-temperature ionic liquids (RTILs) in glycosylation reactions has been of great interest as many of these reactions proceed through a cationic oxocarbenium ion that may interact with the anionic counterpart of the IL.[2b,3]

Due to their low toxicity, non-antigenicity and biodegradability, glycosyl esters have been investigated as potential anti-cancer agents and antibiotics.[4] Other application fields include cosmetics, detergents, oral-care products and medical supplies. Also glycosyl esters can be good donors of glycosylation.[5] Different glycosyl donors,[2b,3] like glycosyl fluorides, glycosyl trichloroacetimidates, thioglycosides, glycosyl diethyl phosphate and unprotected sugars, had been applied in the synthesis of glycosyl esters. Some of the drawbacks to all these donors may include the need for low or high reaction temperatures, use of inert conditions and molecular sieves, lengthy preparation of the donor, the usage of high boiling point solvents like DMF and DMSO,[7,8] modest yields or a low stereoselectivity of C1 conformation.

Despite the many synthetic efforts, there is still a demand for the exploration of green methods that are applicable to both laboratory and industrial scale preparation. This O-glycosylation is not as easy as we imagined. For the reaction couldn't be processed very smoothly for carboxy that shows weak nucleophilicity, assistant measures for improving esterification were demanded. If in the presence of metal ions as promoter glycosyl bromides may be activated under traditional Koenigs–Knorr conditions (Scheme 1). In this paper, glycosylations were carried out with 2,3,4,5-tetra-O-acetyl-α-D-galactopyranosyl bromide **1** as glycosyl donor. Although considered less stable than their fluoride counterpart, glycosyl bromides offer several advantages over other donors. For example, they do not require lengthy preparations and are commercially available.

Ionic liquids have been described as one of the most promising environmentally benign reaction media, which are non-volatile, nonexplosive, recyclable, have kinetic and thermodynamic behavior different from classical solvents. Since many glycosidation reactions go through an oxocarbenium ion, which could interact

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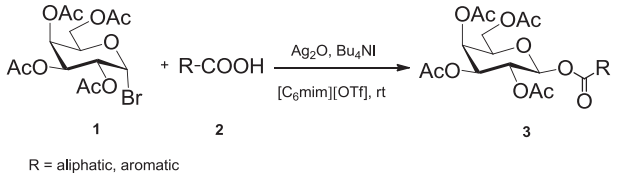
http://dx.doi.org/10.1016/j.carres.2015.01.010
0008-6215/

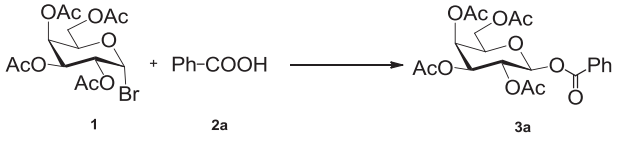


Scheme 1. The synthesis of glycosyl esters.

with an anion species contained in ionic liquid, we speculated that the possibility of stereoselective glycosidation and the improved yield of the reaction induced by ionic liquid would be achieved.[6,9] There are many types of ionic liquids such as N-methyl imidazoles, N-vinyl imidazoles, pyridines, pyrrolidines and quarternary ammonium-based salts. Besides economic considerations and ease in popularizing, imidazolium-based RTILs were focused. To the best of our knowledge, the O-glycosidic bond formation of glycosyl 1-ester supported by ionic liquid has not been reported.

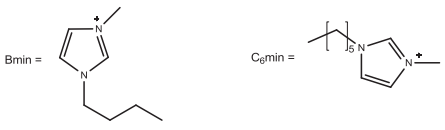
All the reactions were carried out at room temperature without sample pretreatment, inert conditions and molecular sieves. In our initial study, we screened four imidazolium-based RTILs at 25 °C using silver oxide and TBABr as catalysis (Table 1). The reaction in the Bmim·HSO_4 (Table 1, entry **3**) didn't take place. Obviously Bmim·HSO_4 belongs to Brönsted acid that might be adverse to this reaction. Bmim·BF_4 and C_6mim·BF_4 that are part of neutral ionic liquid (Table 1, entry **1**, **2**) afforded the same yield (86%). C_6mim·OTf performed best to lead to the best yield (89%). Thus C_6mim·OTf was chosen as the model RTIL. To compare the catalytic action of the metal salts, a series of catalysts for this reaction was evaluated. As shown in Table 1, Cs_2CO_3, Ag_2CO_3 and Ag_2O (Table 1, entry **4**, **5**, **8**) could run the reaction better than other salts. An intense study for the preference of Cs_2CO_3, Ag_2CO_3 and Ag_2O is underway.

Table 1
Screening of reaction parameters for the synthesis of **3a**



Entry	Ionic liquid[a]	Catalyst	PTC	Yield
1	Bmim·BF_4	Ag_2O	TBABr	86%
2	C_6mim·BF_4	Ag_2O	TBABr	86%
3	Bmim·HSO_4	Ag_2O	TBABr	0
4	C_6mim·OTf	Ag_2O	TBABr	89%
5	C_6mim·OTf	Cs_2CO_3	TBABr	89%
6	C_6mim·OTf	CsF	TBABr	50%
7	C_6mim·OTf	CsOAc	TBABr	69%
8	C_6mim·OTf	Ag_2CO_3	TBABr	87%
9	C_6mim·OTf	$CdCO_3$	TBABr	26%
10	C_6mim·OTf	$K_3PO_4·3H_2O$	TBABr	64%
11	C_6mim·OTf	Rb_2CO_3	TBABr	24%
12	C_6mim·OTf	Ag_2O	TBAF	0
13	C_6mim·OTf	Ag_2O	TBACl	72%
14	C_6mim·OTf	Ag_2O	TBAI	90%
15	C_6mim·OTf	Ag_2O	No PTC	58%

[a] Structure of IL cations:



Ag_2O performed better than Cs_2CO_3, Ag_2CO_3 and was decided as a model promoter for further optimization. Quaternary ammonium salts also displayed a special function in the system. The notable observation was that the yield was poor even when supported by Ag_2O in RTIL (Table 1, entry **15**) if there was no quaternary ammonium salt in the reaction. It verifies that phase transfer catalyst can decrease multiphase's interfacial tension and activate reactants. Diverse halogen of quaternary ammonium salts led to different effects. TBAF hindered the reaction to 0 yield (Table 1, entry **12**), which was worse than in no PTC system (Table 1, entry **15**). Tetrabutylammonium iodine (TBAI, Table 1, entry**14**) achieved better than its chloride and bromide analogues (Table 1, entry **4**, **13**). This trend is correlated with the order of the activity of halides, which increases from chloride to iodine.

The outcomes were all β configuration, which was inferred from the chemical shifts and coupling constants of the anomeric proton signals. Noteworthy, in some IL-mediated glycosylations of the same donor **1**, the α-glycoside was obtained in addition to the β-product.[6b] Poletti et al. showed that the stereoselectivity of a glycosidation using a glycosyl trichloroacetimidate was changed by the ionic liquid.[6c] Luckily β-anomers were exclusive in our mild IL conditions.

The most efficient system was found and a variety of acceptors was tested for the scope and specificity of the methodology (Table 2). With electron-donating groups in aromatic substrates (Table 2, entry **5**, **7**, **9**), the yields were better than ones bearing electron-withdrawing groups (Table 2, entry **11**, **8**, **10**). Comparing the effect of nitro group's position on the benzene ring (Table 2, entry **11**, **8**, **10**), the sequence of the yields was *p*->*m*->*o*-position substrates. Halide groups had different influences to carboxyl groups through the benzene ring (Table 2, entry **3**, **15**, **2**). The bromide and iodine analog' yields were better than chloride ones. We expanded the scope of the substrates to aliphatic acid (Table 2, entry **13**, **12**, **4**, **6**, **14**). To our great surprise butyric acid (Table 2, entry **12**) and cinnamic acids (Table 2, entry **4**, **6**, **14**) all produced excellent yields. Interestingly, we had published the X-ray crystal structures of aliphatic compound **3l** (2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl butyrate). The acetoxymethyl and butyrate groups are located on the same side of the pyran ring, showing the β-configuration for the D-glycosyl ester; the butyl group adopts an extended conformation, the C—C—C—C torsion angle being 179.1°. In the crystal, the molecules are linked by weak C—H···O hydrogen bonds.[10]

Comparison experiments were performed (Table 3). The yield of glycosylation was highly improved when using C_6mim·OTf as solvent. RTIL had a striking contribution to the condensation of glycosyl ester, the yield increased to 93%, relatively 39% in the normal solvent even when promoted by Ag_2O and Bu_4NI (Table 3, entry **1**). It led to the implication that RTIL might be pivotal to the synergistic effect of C_6mim·OTf, Ag_2O and TBAI.

Theoretically the RTILs would enhance the interaction of multiphase involving glycosyl bromide, aliphatic or aromatic acids and Ag_2O. TBAI might assist this solubilization capacity. The correct anionic counterpart of the IL could interact with cationic oxocarbenium ion. Finally the intermediate was attacked by carboxylic ion in a like SN_2 mechanism to generate the specific products. More detailed mechanistic studies to understand the precise role of ionic liquid, TBAI, catalyst and the synergistic effect in these reactions are warranted.

It's the highlight that the C_6mim·OTf is non-volatile, nonexplosive, recyclable. The glycosylation didn't need lengthy preparation, inert conditions and molecular sieves. For recycling of C_6mim·OTf and two promoters the final mixture was loaded directly on silica gel chromatography. The product, the mixture of C_6mim·OTf and promoters were separated due to their polarity. We

Table 2
The products and yields of the condensation of 2,3,4,6-tetra-α-acetyl-D-galactopyranosyl bromide **1** and carboxylic acids **2a**–**2o**

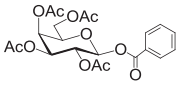
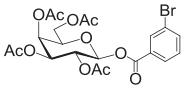
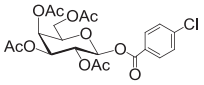
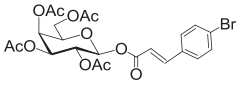
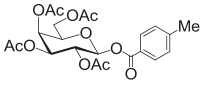
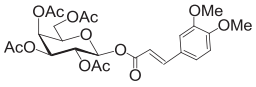
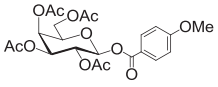
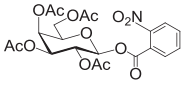
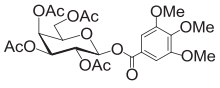
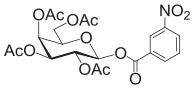
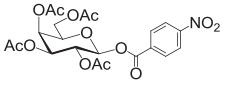
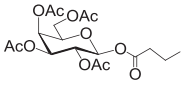
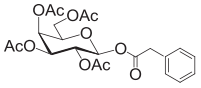
Entry	Donor	Acc.	Product	Yield	α/β ratio
1	**1**	**2a**	 **3a**	90%	β only
2	**1**	**2b**	 **3b**	92%	β only
3	**1**	**2c**	 **3c**	87%	β only
4	**1**	**2d**	 **3d**	94%	β only
5	**1**	**2e**	 **3e**	94%	β only
6	**1**	**2f**	 **3f**	90%	β only
7	**1**	**2g**	 **3g**	96%	β only
8	**1**	**2h**	 **3h**	65%	β only
9	**1**	**2i**	 **3i**	95%	β only
10	**1**	**2j**	 **3j**	75%	β only
11	**1**	**2k**	 **3k**	84%	β only
12	**1**	**2l**	 **3l**	93%	β only
13	**1**	**2m**	 **3m**	81%	β only

Table 2 (*continued*)

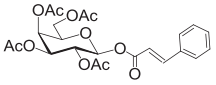
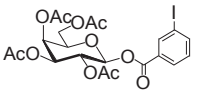
Entry	Donor	Acc.	Product	Yield	α/β ratio
14	**1**	**2n**	 **3n**	94%	β only
15	**1**	**2o**	 **3o**	95%	β only

Table 3
Comparison of the condensation of glycosyl esters[a]

Way	Solvent	Catalyst	PTC	Tem.	Yield%
1	Pyridine	Ag_2O	TBAI	rt	39
2	DCM/H_2O	NaOH	No	rt	10
3	DMF	DMAP	No	0 °C	33
Our method	C_6mim·OTf	Ag_2O	TBAI	rt	93

[a] Reactants: n-butyl acid and 2,3,4,6-tetra-α-acetyl-D-galacto-pyranosyl bromide; identical ratio of reactants.

didn't find any apparent loss in the yield using recycled ionic liquid and promoters. With respect to application of β-glycosyl 1-ester, the Ac groups can be moved selectively by specific catalyst.[11]

In summary the β glycosylation of glycosyl bromide and aliphatic or aromatic acids was achieved in this RTILs enhanced system. The diverse influences to reaction and their synergistic effect were observed. The novel approach is eco-friendly, economic and without strict controls.

1. Experimental

1.1. General procedure for the synthesis of glycosyl ester (*3a*)

All the reaction temperature was at room temperature. Ag_2O (163.8 mg, 0.70 mmol) and TBAI (261.1 mg, 0.70 mmol) were added in the RTIL (1.0 g) and stirred for 1 h. Then benzoic acid (64.1 mg, 0.53 mmol) was added and stirred for 20 min followed by addition of 2,3,4,6-tetra-α-acetyl-D-galactopyranosyl bromide (146.8 mg, 0.35 mmol) to the reaction mixture. The reaction was stirred overnight. After completion of the reaction, the mixture was diluted with 1–2 ml of CH_2Cl_2 and loaded onto a silica gel column for purification by silica gel chromatography using a gradient of Petroleum ether-EtOAc (0–50% EtOAc). The desired product was obtained as white foam.

Corresponding data: 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl benzoate (**3a**): ^{1}H NMR (400 Hz, $CDCl_3$): δ=8.07 (d, 2H, J=7.2 Hz), 7.61 (t, 1H, J=7.6 Hz), 7.47 (t, 2H, J=7.6 Hz), 5.94 (d, 1H, J=8.0 Hz), 5.55 (dd, 1H, J_1=8.4 Hz, J_2=10.4 Hz), 5.50 (d, 1H, J=3.2 Hz), 5.21 (dd, 1H, J_1=3.6 Hz, J_2=10.8 Hz), 4.24–4.14 (m, 3H), 2.20 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H) ppm. ^{13}C NMR (125 Hz, $CDCl_3$): δ=170.1, 170.0, 169.7, 169.3, 164.4, 133.8, 130.0, 128.6, 128.4, 92.6, 71.6, 70.5, 67.7, 66.8, 60.9, 20.42, 20.35 ppm. HSMS: (ESI) m/z $[M+Na]^+$ calcd for $C_{21}H_{24}NaO_{11}$: 475.1216, found: 475.1197.

Acknowledgement

The financial support from the National Natural Science Foundation of China under Grant No. 30870553, the International Science & Technology Cooperation Program of China under Grant No.

2010DFA34370 and the International S&T Cooperation Program of Zhejiang under Grant No.2013C14012 for this work is greatly appreciated. The authors thank Mr. Reggy Ford greatly for his assistance in amending our manuscript.

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